The amendment herein, in fact, cancels claims 1 and 10 and adds new claim 11 which is believed to incorporate the Examiner's thoughts as expressed in the Examiner's interview summary record dated March 31, 1980.

Accordingly, it is requested that the Examiner reconsider his 35 USC 112 and 35 USC 103 rejections in light of the above amendments.

As can be seen, newly added claim 11 specifies the administration of the compound to a diseased host for a specified purpose. Claim 11 also identifies the nature of the "effective amount" of the compound being administered and, as discussed in the meeting with the Examiner, includes the mechanism involved. It is believed that the claims herein fully comply with the requirements of 35 USC 112, paragraph 2 and the rejection accordingly should be withdrawn.

The Examiner is respectfully requested to reconsider his 35 USC 103 rejection of claims 1-10.

The Examiner alleges that reference R teaches the administration of sodium benzoate to man; the conversion of this salt to urinary hippuric acid and the lowering of normal urea and NH_3-H content of the urine is a result thereof.

The Examiner also alleges that reference S teaches that a marked increase of urinary-N (hippuric acid) occurs after the administration of benzoic acid in pigs and that references T and U teach the administration of phenylacetic acid, respectively, to rabbits and man, the latter reference showing urinary glutamine conjugates.

References V and W, according to the Examiner, are cumulative as showing affinity of the applicants' compounds for systemic nitrogen, in vivo, in humans.

The Examiner then concludes it would be obvious to administer the compounds specified in the applicants' claims where it is desired to lower systemic nitrogen or to use these compounds for the treatment of the diseases set forth in the present specification. The applicants respectfully disagree.

For instance, with regard to reference S McCollum and Hoagland, Studies of the Endogenous Metabolish of the Pig as Modified by Various Factors, J. Biol. Chem. 16: 321, 1913-1914), it is the applicants' view that there is no teaching in this publication that pigs which are given a benzoate, have an increased urinary nitrogen excretion. A careful reading of that paper, including Table I, reveals that there was no significant increase in total nitrogen excretion when the pig received any dose of benzoate. Table I, which is a summary of McCollum and Hoagland's investigation, illustrates five periods of study, a control period (I) during which benzoate was withheld and three periods during which benzoate was given in various doses (II-IV) and a period in which HCl was added to the benzoate intake (V). As noted above from the results reported in this table, no significant increase in total nitrogen excretion was observed except for period V during which the pig received HCl. The increase in urinary nitrogen during period V is a result of the expected increase in ammonia excretion because of the acidosis induced by the administered HCl, not because

of the administered benzoate. That such is the case is also concluded by the same authors (McCollum and Hoagland, J. Biol. Chem. 16: 299, 1913-1914 - a companion reference S).

In another study in this latter publication, following a 9-day control period, the investigators treated another pig with 5g. of benzoate for three days and 10g. of benzoate for four days. Table II summarizes their results. Again no significant increase in urinary nitrogen occurred.

Concerning reference V (Shiple and Sherwin, Jour. Am. Chem. Soc. 44: 618, 1922) this publication shows that in man the hourly nitrogen excretion, prior to benzoate ingestion, is 0.3g./hr. Following two doses of 3g. each of benzoate, the hourly nitrogen excretion is essentially unchanged at 0.325g/hr. and 0.2g/hr. However, in applicants' view even those studies in man may not be appropriate because the subjects under study were receiving a very low protein intake and were not suffering from a nitrogen accumulation disease.

In this same publication, the authors, commenting on the paper of McCollum and Hoagland, supra, concluded that "...the ingestion of benzoate does not affect the creatinine output, and little the total nitrogen...".

Reference V (J. Am. Chem. Soc. 44: 618, 1922) also teaches that when a man was given 4 or 6 grams of phenylacetate there was little change in total urinary nitrogen excretion at a time that urinary urea nitrogen decreased.

The Examiner will also note, with regard to the pig studies noted above, that the benzoate given there was under circumstances quite unrelated to the applicants' use of benzoate in man. The pigs under study were receiving no nitrogen intake whereas the applicants use the benzoate in humans who not only are receiving nitrogen, but importantly are also suffering from nitrogen accumulation.

The Examiner has raised two objections which appear to be internally contradictory. On the one hand, the Examiner cites the pig data of reference S (J. Biol. Chem. 16: 321, 1913) concluding that benzoate administration leads to increased nitrogen excretion, and on the other hand, the Examiner states that reference R teaches that in man the normal urea and NH_3-H content of the urine is lowered as a result of the conversion of benzoate to urinary hippurate. Clearly under the latter circumstances in man total urinary nitrogen excretion remains constant at a time that the partition of urinary nitrogen changes (see reference R and reference V).

In the more relevant studies in man the evidence is conclusive that neither benzoate nor phenylacetate administration leads to an increased nitrogen excretion. Lewis (Jour. Biol. Chem. 18: 225, 1914) found that after a man ingested 10g. of benzoate his urinary nitrogen excretion increased 6.8%, an amount within the normal day-to-day variation and well within experimental error.

The Examiner cites reference T (Hijikata, Y. The Influence of Putrefaction Products on Cellular Metabolism, 11. On the influence of phenylacetic acid

and phenylpropionic acids on the distribution of nitrogen in the urine. J. Biol. Chem. 51: 141, 1922) wherein it is suggested that administration of phenylacetic acid to rabbits leads to an increase in urinary nitrogen. An inspection of that article, particularly tables II, III and IV does show an increase in urinary nitrogen after the administration of phenylacetic acid but that in all three experiments 80% of the increase was accountable by urea nitrogen rather than an amino acid conjugation product of phenylacetic acid. This increased urea nitrogen output supports the conclusion by Hijikata that there was a decomposition of tissue protein presumably caused by the administered phenylacetic acid.

Thus, in no way can reference T be construed to be instructive in the use of phenylacetic acid in man for the treatment of nitrogen accumulation diseases.

The applicants thus submit that none of the art relied on or discussed which studies the effect of benzoate on nitrogen balance reveals any significant effect on net nitrogen balance. Furthermore, there are no data in these references which reveals or discloses the effect of benzoate on nitrogen balance in humans suffering from a nitrogen accumulation disease.

The applicants submit, accordingly, that the results embodied in Figures 2 and 3 of the present specification, showing increases in total urinary nitrogen of 35% and 43% following administration of benzoate and phenylacetic acid, respectively, to a patient suffering from a nitrogen accumulation disease, are entirely new and unexpected.

The present invention is directed to a method for treating nitrogen accumulation diseases by promoting waste nitrogen via latent endogenous biochemical pathways. Heretofore, the treatment of nitrogen retention relied on the qualitative and quantitative manipulation of dietary nitrogen (Close, J., The Use of Amino Acid Precursors in Nitrogen Accumulation Disease, New Eng Med 290: 663, 1974; Walser, M., The Conservative Management of the Uremic Patient, in The Kidney, Vol. II, Brenner, B. M. and Rector, F.C. eds. W.B. Saunders, 1976; Sherlock, S., Disease of the Liver and Biliary Systems, 5th ed. Blockwell 1975; and Shih, V., Urea Cycle Disorder in The Metabolic Basis of Inherited Disease, Stanbury, J., Wyndgaarden, J. and Fredrickson, D. eds. McGraw-Hill, 1978).

A copy of each of the references referred to above is enclosed.

In conclusion, it is submitted that none of the prior art suggests or teaches the applicants' invention and the rejection based thereon should be withdrawn.

In view of the above amendments and remarks, reconsideration and allowance of the claims are respectfully requested.

Respectfully submitted,

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